

REMARKS

In the Office Action dated March 11, 2003, claims 1-3, 6-18, 20-26, 28-30, 32 and 34-55 are pending and are under consideration. Claims 2, 3, 16, 17, 18 and 45 are objected to under 37 C.F.R. § 1.75(c) as allegedly in improper form. Claims 1, 6-15, 20-26, 28-30, 32, 34-44 and 46-55 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1, 6-15, 20-26, 28-30, 32, 34-44, and 46-55 are also rejected under the written description requirement of 35 U.S.C. §112, first paragraph.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 2, 3, 16-18 and 45 are objected to under 37 C.F.R. § 1.75(c) as allegedly in improper form. The Examiner states that a multiple dependent claim cannot depend upon claims which are not preceding claims.

In response, claims 2-3 and 16-18 have been canceled. The subject matter of original claims 2-3 and 16-18 are now delineated in new claims 56-60, respectively. Claim 45 has been amended to depend from claim 44, instead of claim 2. As such, the objection to claims 2-3, 16-18 and 45 is overcome. Withdrawal of the objection is therefore respectfully requested.

Claims 1, 6-15, 20-26, 28-30, 32, 34-44 and 46-55 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

The Examiner contends that the claims are vague in the recitation of leukemia inhibitory factor (or "LIF"), which is used as the sole means of identifying a constituent of the claimed compositions. The Examiner states that different laboratories may use the same laboratory designation "LIF", to define completely distinct inhibitory factors. Citing the abstract

of Van Vlasselaer et al., *Prog Growth Factor Res* 4: 337-353 (1992), the Examiner states that the art recognizes LIF as a synonym for at least nine different factors. The Examiner also contends that it is unclear as to whether the claims are limited to one particular LIF or encompass all known LIFs in humans and animal species as well as LIFs yet to be discovered. The Examiner suggests amending the claims to include a unique identifier, such as a sequence identifier.

Applicants respectfully submit that a principle feature of the present invention resides in the identification of components and a process for making a composition containing a LIF protein or derivative, which exhibits an improved chemical and physical stability. Therefore, the present invention provides LIF-containing compositions with improved stability and methods of preparing such compositions. The claimed compositions and methods are not limited to any particular LIF protein for any particular species, but encompass all LIFs from human and other animal species.

Applicants further respectfully submit that at the time when the application was filed in November 1997, the term "LIF" was commonly used in the art and was understood by one skilled in the art to uniquely identify proteins from various animal species, which are characterized by certain structural and functional features. It is observed that the Van Vlasselaer et al. article itself, published in 1992 (i.e., five years before the priority date of the instant application), recognized that the nine different factors referred therein were all in fact LIF. The Examiner's attention is also directed to Hilton D. J., "LIF: Lots of interesting functions", *TIBS*, 17:72-76, 1996 (attached hereto as **Exhibit A**), which confirms that the following are alternative names for LIF, identified from different animal species: differentiation inducing factor (DIF, from human), differentiation stimulating factor (D-factor, from murine), differentiation inhibitory activity (DIA, from rat), differentiation retarding factor (DRF, from murine), cholinergic

neuronal differentiating factor (CNDP, from rat), human interleukin for DA cells (HILDA, from human), hepatocyte stimulating factor-III (HSF-III, from human), and melanocyte derived lipoprotein lipase inhibitor (MLPLI, from human). See, in particular, Table 1 of the Hilton reference. Applicants are also providing a copy of a review article, published in 1997 in Oxford University Press "A Guide to Cytokines and Their Receptors" edited by Nicos A. Nicola, p124-126, "Leukemia Inhibitory Factor (LIF)" (**Exhibit B**), which outlines the structural and functional features of LIF proteins from various animal species, including human, murine, rat and porcine.

In addition, Applicants respectfully submit that the sequences and recombinant production of murine and human LIF are disclosed in the International Patent Applications PCT/AU88/00093 (**Exhibit C**) and PCT/AU90/00001(**Exhibit D**), as referenced in the present specification at page 5, line 4.

Therefore, Applicants respectfully submit that the term "LIF", as recited in the present claims, is unambiguous and clearly understood by those skilled in the art. As such, it is respectfully submitted that the rejection under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is therefore respectfully submitted.

Claims 1, 6-15, 20-26, 28-30, 32, 34-44, and 46-55 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

According to the Examiner, the specification does not provide any particular definition for "leukemia inhibitory factor". The Examiner states that the art recognizes LIF as a synonym for at least nine different factors, defined on the basis of their effect on a variety of cell

types including lymphomas, liver cells, embryonic stem cells and carcinoma cells. The Examiner states that LIFs are also structurally related to cytokines such as IL-6, oncostatin M, ciliary neurotrophic factor, IL-11 and cardiotrophin-1, and have redundant activities with these other cytokines. Thus, the Examiner contends that the terms “LIF”, “derivatives” and “homologs”, as recited in the claims, are drawn to a genus of proteins which include IL-5, oncostatin M, ciliary neurotrophic factor, IL-11, cardiotrophin-1, as well as LIFs from other species, allelic variants, mutants and LIFs as yet to be discovered. It is the Examiner’s opinion that the specification fails to teach the common structural attributes of members of the claimed genus. It is also the Examiner’s opinion that the specification also fails to place a limitation on the specific functional characteristic of the claimed genus, and the art teaches that the LIF proteins have pleiotropic effects, and are active on a wide variety of cell or tissue types. Therefore, the Examiner contends that one skilled in the art could not determine whether a given protein was excluded or included within the claimed genus.

As submitted above, the term “LIF” was commonly used by one skilled in the art to uniquely identify proteins from various animal species, which are characterized by certain structural and functional features. Its meaning is unambiguous and clearly understood by those skilled in the art.

Although it may be the case that certain functions of LIF overlap with those of some other cytokines, Applicants respectfully submit that, as understood by those skilled in the art and as evidenced by the articles attached hereto as Exhibits **A-B**, LIF is a group of proteins uniquely identified by its structural and functional features, which distinguish LIF from other cytokine molecules.

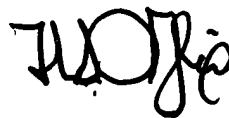
Applicants further respectfully submit that Applicants are not claiming an isolated

LIF molecule in the present application. Rather, the present invention is directed to a composition containing LIF, which exhibits improved stability and is characterized by containing a stabilizing agent and additives for maintaining pH and isotonicity, wherein the pH of the composition is between about 3.5 and 6.5. Applicants need not teach in detail what is known by those skilled in the art. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). In this regard, at the time the present application was filed, multiple LIF molecules had been characterized in terms of their structural and functional features. See, e.g., Hilton (**Exhibit A**), Nicola (**Exhibit B**), PCT/AU88/00093 (**Exhibit C**) and PCT/AU90/00001 (**Exhibit D**).

Therefore, it is respectfully submitted that the present claims fully satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Frank S. DiGiglio
Registration No. 31,346

SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

FSD/XZ:ab

Enc.: Exhibits A-D